EPIDEMIOLOGY, CLINICAL PROFILE AND ETIOLOGY OF RECURRENT WHEEZE IN CHILDREN BELOW 5 YEARS

Dissertation submitted to

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations

for the award of degree of

M.D DEGREE (PAEDIATRICS) BRANCH VII

INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN MADRAS MEDICAL COLLEGE

APRIL 2012

CERTIFICATE

This is to certify that the dissertation titled, **"Epidemiology, clinical profile and etiology of recurrent wheeze in children below 5 years"** submitted by **Dr.U.Sridhurga,** to the Faculty of Paediatrics, The Tamilnadu Dr.M.G.R Medical University, Chennai, in partial fulfillment of the requirements for the award of M.D. Degree (Paediatrics) is a bonafide research work carried out by him under our direct supervision and guidance, during the academic year 2009-2011.

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DECLARATION

I, **Dr.U.Sridhurga**, solemnly declare that the dissertation titled **"**Epidemiology, clinical profile and etiology of recurrent wheeze in children below 5 years" has been prepared by me.

This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in Paediatrics.

Place : Chennai

Date : **Dr.U.SRIDHURGA**

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CERTIFICATE OF APPROVAL

To
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PG in MD Paediatrics
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Dear Dr. U. Sridhurga

The Institutional Ethical Committee of Madras Medical College reviewed and discussed your application for approval of the project / proposal / clinical trail entitled " Epidemiology , Clinical profile and Etiology of Recurrent wheeze in children below 5 years" No 60082010.

The following members of Ethical committee were present in the meeting held on 24.08.2010 conducted at Madras Medical College, Chennai -3.

1. Prof. S.K. Rajan, MD	-- Chairperson
2. Prof. J. Mohanasundaram, MD,Ph.D,DNB Dean, Madras Medical College, Chennai -3	-- Deputy Chairman
3. Prof. A. Sundaram, MD Vice Principal , MMC, Chennai -3	-- Member Secretary
4. Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
5. Prof. C. Rajendiran , MD Director, Institute of Internal Medicine, MMC, Ch-3	-- Member -- Member
6. Prof. Md. Ali, MD, DM Professor & Head ,,Dept. of MGE, MMC, Ch-3	-- Member -- Member
7 Prof. Shantha Ravishankar, MD Professor of Neuro Pathology, MMC, Ch-3	-- Member
8. Tmt. Arnold Soulina	-- Social Scientist

We approve the trail to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

SPECIAL ACKNOWLEDGEMENT

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CONTENTS

INTRODUCTION

The incidence of wheeze is very high in children, approximately 25 to 30 % of infants will have had at least one wheezing, by 3 years of age an episode of wheeze will have occured in 40 % of children and 50% will have atleast one episode of wheezing by 6 years (1) .

In India the incidence of wheeze is high in children . It has been found that one in three children have their first episode of wheeze in infancy, and the prevalence of wheeze is nearly 50% by 6 years of age . 25% of children who develop persistent asthma started to wheeze by age of 6 months and 75% by 3 yrs of age (2).

A wheeze is defined as a musical and continuous sound that originates from oscillations in narrowed airways. Wheezing is more common in expiration as a result of critical airway obstruction(3). Children presenting with more than or equal to three episodes of wheeze in an year are called recurrent wheezers (4).

Children differ from adults that they are more prone for wheeze due to the following reasons

- Infants are more prone to wheeze due to

1. Compliant chest wall, the inward pressure produced during expiration subjects the intrathoracic airway to collapse.
2. The differences in tracheal cartilage composition and airway smooth muscle make them more prone for collapse.

These conditions abate by 1st year of life.

In children less than 5 years small calibre peripheral airways contribute to 50% of total airway resistance. Resistance to airflow is inversely related to the radius to the 4th power. Hence marginal additional narrowing in this children causes further flow limitation and a subsequent wheeze.

Unlike adults, in children there are variety of causes for wheeze.Depending on the etiology the treatment varies, even it may prove detrimental if treated inappropriately.

For example airway malacia when treated with beta agonists which is commonly used to treat wheeze may be detrimental.

There exists a group of infants and toddlers who are born with anatomically small airways. This predisposes them to wheeze with viral infections (wheeze associated with lower respiratory infections). Each viral infection results in an inflamed hyperreactive airway and further narrowing of airway caliber. As these infants grow older, the airways grow in size and the symptoms progressively abate. Thus, not all wheeze and cough are caused by asthma.

The diverse etiology are as follows

Infection

- Viral

  Respiratory syncytial virus (RSV)

  Parainfluenza

  Adenovirus

  Influenza

  Rhinovirus

  Other

- Bacterial

  Chlamydia trachomatis

  Tuberculosis

- Fungal

  Histoplasmosis

Anatomic Abnormalities

- Malacia of the larynx, trachea, and/or bronchi
- Tracheoesophageal fistula (specifically H-type fistula)

Extrinsic compression

- Vascular ring or sling
- Mediastinal lymphadenopathy from infection or tumor
- Mediastinal mass/tumor
- Airway hemangioma
- Cystic adenomatoid malformation
- Bronchial/lung cyst
- Congenital lobar emphysema
- Aberrant tracheal bronchus
- Sequestration
- Congenital heart disease with left-to-right shunt (increased pulmonary edema)

Inherited

- Cystic fibrosis
- Immunodeficiency states
- IgA deficiency
- B-cell deficiencies
- Primary ciliary dyskinesia
- Neonatal AIDS
- Bronchiectasis

Aspiration Syndromes

- GERD
- Pharyngeal/swallow dysfunction

Other Causes

- Bronchopulmonary Dysplasia
- Interstitial Lung Disease like Bronchiolitis Obliterans
- Foreign Body

Of these the most common cause of wheeze in children under 5 years are viral infection, asthma, airway anomalies like traceomalacia, other rare airway anomalies like vascular rings are also reocognised with the advent of bronchoscopy. Other causes of wheeze are retained foreign body, gastroesophageal reflux disease, other immunodeficiency disorders leading to impaired clearance of secretion and predisposition to recurrent infection.

1. The most common chronic disease of childhood is **asthma** and it causes maximum morbidity which is indicated by frequent hospitalisation due to exacerbation and abstineesm (5). Asthma is defined as chronic inflammatory disease of the airway characterised by airway hyperresponsiveness which causes recurrent episodes of wheeze, breathlessness, cough, chest tightness. But in children under 5 years the symptoms are variable and non specific. Further it is difficult to assess airway hyper responiveness and inflammation in this age group. Hence to aid in diagnosing asthma based on symptoms various wheeze phenotypes have been defined.

Wheeze in under 5 children have been classified in various ways

Based on the duration of wheeze the classification is as follows. This is useful only in population studies, not in clinical practice (6).

Transient wheeze: It includes children started having wheeze before the age of 3 years and are found (retrospectively) to have disappeared by the age of 6 years (transient wheeze may be episodic viral wheeze or multiple trigger wheeze)

Persistent wheeze: Symptoms that are found (retrospectively) to have continued until the age of 6 years and older (persistent wheeze may be episodic viral wheeze or multiple trigger wheeze)

Late onset wheeze: Wheeze that starts after the age of 3 years (late onset wheeze may be episodic viral wheeze or multiple trigger wheeze)

Temporal pattern of wheeze which is useful in clinical practice (7)

Episodic (viral) wheeze: Wheezing occurs during discrete episodes, and it is associated with a viral cold; no wheeze between episodes.

Multiple trigger wheeze: In this group child has discrete exacerbations, but also wheezes between episodes.

To aid in diagnosis of asthma , Asthma Predictive Index has been proposed , preschool children with recurrent wheeze for 1 year with one major criteria or two minor criteria has 97 % specificity and 77 % positive predictive value (8).

Major criteria

- Parent asthma
- Eczema
- Inhalant allergen sensitization

Minor Criteria

- Allergic Rhinitis
- Wheezing apart from colds
- Eosinophils > 4%
- Food allergen sensitization

- The evaluation to confirm the diagnosis sometimes requires a therapeutic trial.
- When a child is seen with expiratory wheezing and increased work of breathing who has impressive response to a bronchodilator, this is obviously supportive of the diagnosis. But particularly with viral respiratory infection–induced symptoms, where the inflammatory component of airway obstruction with mucous secretion and mucosal edema predominate, a therapeutic trial of a systemic corticosteroid becomes an effective means to provide support for the diagnosis.
- Allergy skin testing is a quick and useful evaluative means of assessing the potential role for specific IgE to inhalant allergens in a child with asthma. There is a common belief that allergy skin testing is not useful in this age group. However, there is extensive documentation of the presence of allergic antibody demonstrable with allergy skin testing in the preschool child and even in infancy. The presence of specific IgE to inhalant allergens can identify the young child with asthma who has a potential for an allergic component to his or her disease. Even

when not correlating with symptoms in a child with the common pattern of viral respiratory infection–induced asthma at the time initially evaluated, the presence or absence of specific Ig E to inhalant allergens provides prognostic information regarding those children at greater risk for developing persistent symptoms (9).

- From the history, physical findings, response to treatment, and allergy skin testing, the diagnosis can be confirmed, the pattern of asthma identified, and the prognosis for continued symptoms reasonably predicted.
- When the findings raise doubts about the diagnosis of asthma, alternative diagnoses can be considered and appropriate diagnostic tests undertaken.
- Many studies have reported that nasal symptoms occur in 28% to 78% of patients with asthma as compared with approximately 5% to 20% of the general population.

2. Yet another common cause of recurrent wheeze in under 5 children which is under diagnosed is **airway anomaly**.

- Congenital airway malacias are increasingly encountered in children . The incidence reported in western literature is between 1: 1500 and 1: 2500 (10) .
- The word Malacia means “softness” and, in medical terminology, it refers to cartilage or bone. Tracheomalacia is weakness of trachea due to reduction and atrophy of the longitudinal elastic fibers of the pars membranacea, or impaired cartilage integrity, which makes the airway softer and more susceptible to collapse (11) .
- The normal intrathoracic trachea dilates during inspiration and narrows during expiration due to the difference between intrathoracic and intraluminal pressures.In tracheomalacia, this normal physiology is exagerrated. In intrathoracic tracheomalacia narrowing is exaggerated when intrathoracic pressure exceeds the intraluminal pressure, during forced expiration, cough, or the Valsalva maneuver.

- In case of extrathoracic or cervical tracheomalacia negative intrapleural pressure is transmitted to extrathoracic trachea which causes the upper airway to collapse due to pleural reflection ,during inspiration.
- Tracheomalacia can be localized or it involve the entire trachea.
- The term tracheobronchomalacia is used when the mainstem bronchi is also involved.
- The weakness and collapsibility of one or both of the mainstem bronchi without the involvement of trachea is called bronchomalacia. It is less common than tracheomalacia and tracheobronchomalacia.

Symptoms of Pediatric Tracheomalacia

- Stridor
- Barking cough
- Respiratory distress
- Wheeze
- Anoxic spells
- Cyanosis
- Bradycardia
- Tachyarrhythmias
- Spontaneous hyperextension of the neck
- Prolonged expiratory phase
- Breathholding spells
- Failure to thrive
- Increased work of breathing
- Sternal, substernal, and intercostal retractions
- Recurrent pulmonary infections
- Reflex apnea
- Respiratory arrest
- Cardiac arrest

3. **External vascular compression** includes a vascular ring, in which the trachea and esophagus are surrounded completely by vascular structures, or a vascular sling, in which the trachea and esophagus are not completely encircled.They can also present with recurrent wheeze.

4. **Gastroesophageal reflux** can cause wheezing with or without direct aspiration into the tracheobronchial tree. Without aspiration, the reflux is thought to trigger a vagal or neural reflex, causing increased airway resistance and airway reactivity. Aspiration from gastroesophageal reflux or from the direct aspiration from oral liquids can also cause wheezing.

5. **Foreign body aspiration** can cause acute or chronic wheezing. Infants who have atypical histories or misleading clinical and radiologic findings can receive a misdiagnosis of asthma or another obstructive disorder as inflammation and granulation develop around the foreign body. Esophageal foreign body can transmit pressure to the membranous trachea, causing compromise of the airway lumen.

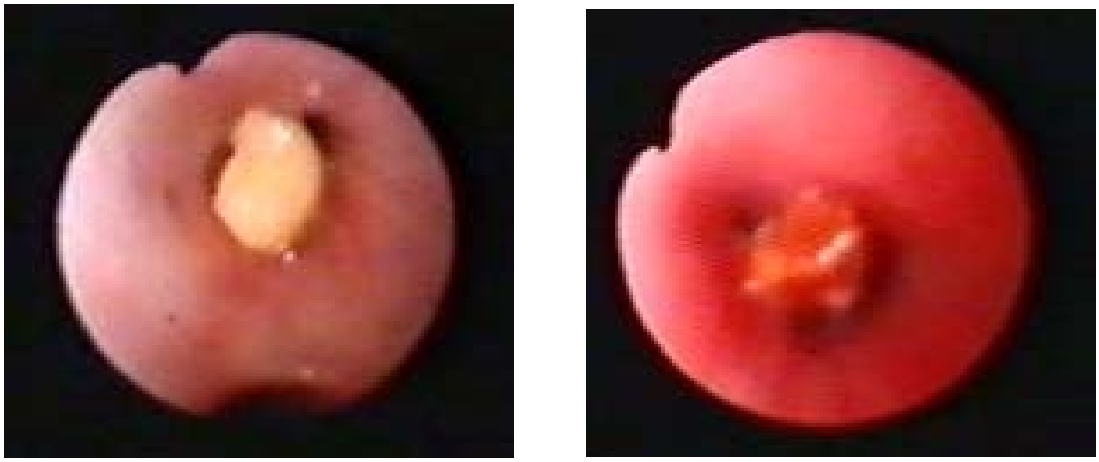

Fig 1 Bronchoscopic picture showing retained foreign body

Statistics at ICH & HC:

Children presenting with wheeze during 1 year period

- Wheeze associated lower respiratory tract infection 517
- Tracheomalacia 54
- Laryngomalacia 240
- Bronchomalacia 13
- Bronchopneumonia with wheeze 13
- Asthma 275
- Allergic bronchitis 23
- Misc 50

Of these about 5 to 10 % cases present as recurrent wheezing.

REVIEW OF LITERATURE

S. Saglani , et al (12) from London recruited children aged between 3 months and 5 yrs with severe recurrent wheezing, who had been referred to a tertiary centre . They were subjected to investigations including a chest computed tomography scan, blood tests, nasal ciliary brushings, fibreoptic bronchoscopy, bronchoalveolar lavage (BAL), endobronchial biopsy and passage of an oesophageal pH probe.

Results:

A total of 47 children (25 males) with a median age of 26 (range 5–58) months underwent investigation.

- 39% atopic
- Two-thirds had evidence of gastro-oesophageal reflux
- 37 out of 47 had an abnormal bronchoscopy.

Bronchoscopy findings included

- Excessive mucus (20 out of 37)
- Structural abnormalities (13 out of 37)

- Macroscopic inflammation (10 out of 37).
- BAL revealed bacterial growth in 12 out of 44 (27%) patients.
- Out of the endobronchial biopsies obtained from 36 out of 46 (78%) patients
  - 44% had tissue eosinophila
  - 28% had a thickened reticular basement membrane.

Stephanie J. London, *et al* (13) studied the relation between family history and the risk of early onset persistent, early onset transient and late onset asthma which was a descriptive study with sample size 6259. Early onset persistent asthma was associated more strongly with parental history of asthma than either early onset transient or late onset asthma Parental history of allergy was associated most strongly with early onset persistent asthma and least strongly with early onset transient asthma.

Franca Rusconi, *et al* (14) from Italy studied the relation between wheezing conditions and familial, pre-, peri-, and postnatal risk factors which was a descriptive study with a sample size 16,333. Maternal history of asthma or chronic obstructive airway disease,

smoking during pregnancy were significantly ($p < 0.0001$) more associated with persistent wheezing than with transient early and late-onset wheezing. There was a stronger ($p < 0.0001$) positive association between personal history of eczema or allergic rhinitis and persistent and late-onset wheezing than transient early wheezing.

Ruben B, *et al* (10) from Netherland analyzed all flexible bronchoscopies performed during the period from 1997 to 2004 in the Sophia Children's Hospital, and he summarized clinical features of children with primary airway malacia, estimated the incidence of primary airway malacia, and calculated the predictive value of a clinical diagnosis of airway malacia by pediatric pulmonologists.

Bronchoscopy was done in 512 children,of which airway malacia was diagnosed in 160 children (94 males) at a median age of 4.0 years (range, 0 to 17 years). Airway malacia was further classified as primary (136) and secondary (24) children. The incidence of primary airway malacia was found to be 1 in 2,100. When airway malacia was expected based on symptoms, history, and lung function prior to bronchoscopy, this was correct in 74% of the cases. In 52% of the airway malacia diagnoses, the diagnosis was not suspected prior to

bronchoscopy. Airway malacia is difficult to diagnose based on clinical features which has overlap with other more common pulmonary diseases. The auhor recommends bronchoscopy in patients with impaired exercise tolerance, recurrent lower airways infection, and therapy-resistant, irreversible, and/or atypical asthma to rule out airway malacia.

Table 1Airway anomaly in the study done by Ruben , *et al*

Sample size	136
Study population	0 to 17 years
Male/female ratio	1.4:1
Larymgomalacia	0
Tracheomalacia	63(46)
Tracheobronchomalacia	49(36)
Bronchomalacia	24(18)
External compression	0

Ngoc P, *et al* (15) from Boston studied the association between early wheeze and asthma at 7 years of age in children with parental history of asthma or allergies . History regarding wheeze was collected bimonthly from birth to age 24 months and every 6 months thereafter.

Results: Out of the 440 children

- 223 (50.7%) presented with 1 episode of wheeze before 3 years old
- 111 (26.0%) were found to have recurrent early wheeze
- 12 (2.7%) of the children were frequent early wheezers.
- 31 (13.9%) of 223 children with 1 report of wheeze later developed asthma at 7 years of life.
- 24 (21.6%) of 111 children who had recurrent early wheeze had asthma at 7 years of age.
- Among the 12 children with frequent early wheeze, 6 (50%) had asthma at 7 years of age.

Conclusion : Recurrent early wheeze in children who are at risk for atopy had a fourfold increase in the odds of asthma at 7 years of age, and frequent early wheeze had 12-fold increase in the odds of asthma at 7 years of age. Most (94%) of the children without frequent early wheeze did not develop asthma at 7 years of age.

The absence of recurrent early wheeze indicates that at school age there was very low risk of asthma among children with parental history of asthma or allergies.

Cooney, *et al* (16) reported from Canada out of the 723 children found that there was significant association between atopy and parent reported wheeze ever (OR 2.16; 95% CI 1.59-2.94), physician-noted wheeze with a cold (OR 2.23; 95% CI 1.65-3.00) and without a cold (OR 1.82; 95% CI 1.33-2.50). Physician-noted wheeze without a cold was more strongly associated with atopy in girls (OR 2.41; 95% CI 1.48-3.93) compared to boys (OR 1.46; 95% CI 0.96-2.22). In the absence of asthma, the association between atopy and parent-reported wheeze ever, physician-noted wheeze with a cold and without a cold was lost.

Atopy is an important diagnostic marker in the paediatric clinical assessment of wheeze.

Patra S, *et al* (17) from Pakistan found that out of 67 children less than 2 years of age with recurrent wheeze, the male-female ratio was 9:2. The majority of these cases (82%) had onset of wheezing at less than 1 year of age. Out of these 33% were diagnosed as asthma and viral infection associated wheeze.

Patra S , *et al* (18) from India found that wheezing is common among infants and young children because of peculiar anatomical and physiological properties of their lungs. Gastro-oesophageal reflux (GER) has been found as one of the causes wheezing in this age group. Sixty-seven children of less than 2 years age with recurrent or persistent wheezing were evaluated for GER.

- Asthma and wheeze associated lower respiratory tract infection (WALRI) was diagnosed in about 1/3 each of the patients.
- GER studies were positive in over one-third (25/67) of cases.
- Forty-two percent of children who wheezed by 1 year of age had a positive GER study.

The severity of wheezing was higher among those who had GER versus those who did not ($p \leq 0.048$; OR: 3.2) but only 32% patients showed significant response to anti reflux treatment alone while others had partial response.

GER, therefore, is an important cause for recurrent wheezing among children less than 2 years of age, either singularly or as a co-morbidity. The study findings justify investigations for GER among early wheezers; particularly for those who have onset of symptoms by 12 months of age or those who have severe disease.

Sheik , *et al* (19) from USA studied the incidence of GER in 84 healthy infants who were referred to the Pediatric Pulmonary Medicine Division at Kosair Children's Hospital for evaluation of daily wheezing, and followed their clinical course for 18 months.

Fifty-four of 84 (64%) of the population had positive esophageal pH studies (GER-positive group), 24 of them (44%) had no gastrointestinal symptoms suggestive of GER.

30 had normal esophageal pH studies (GER-negative group). Twenty-two of these 30 (73%) infants without GER required nebulized flunisolide, compared to 13 of 54 (24%) infants with GER ($P < 0.0005$).

Thirty-five of 54 (64.8%) infants with GER were able to discontinue all daily asthma medications within 3 months of starting antireflux therapy, while none of the infants without GER were able to discontinue daily asthma medications during the follow-up period ($P < 0.0005$).

Stoddard JJ, *et al* (20) from the University of Wisconsin quantitatively assessed environmental tobacco smoke exposure from parental smoking as a risk factor for asthma or wheezing in childhood, The National Medical Expenditure Survey included 7,578 children and youth less than 18 years of age in a stratified cluster sampling of US households. The study indicates that maternal smoking is responsible for approximately 380,000 excess cases of childhood asthma/wheezing lower respiratory tract illness or 7.5% of the total number of such symptomatic children.

Neuspiel DR, *et al* (21) from New York studied the contribution of parental smoking to wheezing in children in a subset of all British births between April 5 and 11, 1970 (N = 9,670). Children of smoking mothers had an 18.0 per cent cumulative incidence of post-infancy wheezing through 10 years of age, compared with 16.2

per cent among children of non smoking mothers (risk ratio 1.11, 95% CI: 1.02, 1.21). There was a 14 per cent increase in childhood wheezy bronchitis when mothers smoked over four cigarettes per day, and a 49 per cent increase when mothers smoked over 14 cigarettes daily.

STUDY JUSTIFICATION

There are many children getting admitted with recurrent wheezing < 5 years. This study could help in identifying the etiology and other risk factors predisposing these children to wheeze compared to other children.

The exact proportion of various causes of wheeze are not yet published in Indian population. Causes for recurrent wheeze in infants, toddlers and preschool children may vary that needs to be emphasized.

Institute of Child Health and Hospital for Children , Chennai is a place where all the specialities function under one umbrella , even rare causes of recurrent wheeze like airway malacia , GERD , immunodeficiency , missed foreign body are diagnosed .So it is the need of the hour to find the exact proportion of diverse etiology of recurrent wheeze in this age group.

AIM OF THE STUDY

To study the epidemiology, clinical profile and etiology of recurrent wheezing in children less than 5 years who are attending an urban referral centre.

SUBJECTS AND METHODS

i.Methodology

- **Study design**

  Descriptive study.

- **Study place**

  Department of pulmonology and Medical ward ICH & HC , Chennai.

- **Study period**

  August 2010 to October 2011.

- **Study population**

  Any child less than 5 years of age presenting with recurrent wheeze.

- **Case definition**

  Children presenting with more than or equal to three episodes of wheeze in an year are called recurrent wheezers

- **Inclusion criteria**

    1. Age < 5 years
    2. Diagnosed as a case of recurrent wheezer by physician based on history and clinical features.

- **Exclusion criteria**

    1. Parents not consenting for study.
    2. Associated chronic illness.

- **Sample Size**

    All children with the above inclusion criteria who presented during the study period (104 cases).

Ethical committee clearance was obtained from the Institutional Ethical Committee.

ii.Manoeuvre

Cases are recruited based on inclusion and exclusion criteria after obtaining informed parental consent.

History

A detailed history was taken for all patients regarding the age when they entered the study, sex, age of onset of symptoms, presence of the following symptoms like breathlessness, cough, fever which commonly occurs in viral induced wheeze,etc were asked. Symptoms suggestive of upper airway narrowing like noisy breathing, snoring, recurrent aspiration which can be seen in GERD, airway malformation like TEF were asked .H/O foreign body aspiration was also asked since retained foreign body can also present with recurrent episodes of wheeze. Similar episodes in past ,hospitalisation was enquired to define the magnitude of the problem. H/O nebulisation and response to bronchodilator were asked since it helps both to diagnose and treat.H/o atopy both personal and in family were asked.Neonatal history , history on breast feeding , development history and exposure to environmental agents like passive smoking, pollen exposure, exposure to industrial waste were asked.

All these were entered in prestructured proforma

Investigations

Based on the history all children were subjected to investigations. All children underwent basic investigations like complete hemogram and chest X ray. Further investigations like barium swallow, upper GI endoscopy, paranasal sinus imaging were done based on the clinical scenario. Bronchoscopy was planned for all children.

Bronchoscopy

Bronchoscopy is a procedure where the tracheobronchial tree is directly visualised. Flexible Fiberoptic Bronchoscopy is performed in an awake patient under local anaesthesia . The bronchoscope is passed through the nose, between the vocal cords and into the trachea. The bronchoscope could be easily flexed and hence it is easy to visualize airways upto the level of subsegmental bronchi.

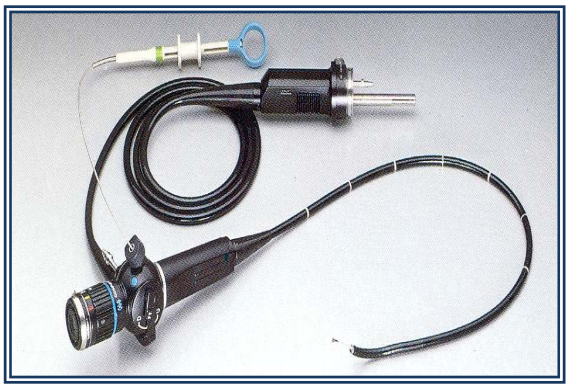

Fig 2 Fiberoptic Bronchoscope

iii .Statistical analysis

The proportion of various outcome measures were arrived. For comparing the clinical features among children with airway anomaly and no airway anomaly , statistical significance was arrived at using Chi Square test . p value < 0.05 is considered significant.

OBSERVATIONS

104 Children with recurrent wheeze were studied in the age group less than 5 years.

Demographic characteristics

Total no. of males = 57(54.8%)

Total no. of females = 47(45.2%)

No predilection to sex was observed

Table 2 Age & sex distribution in study population

Age (Years)	Male n (%)	Female n (%)	Total n (%)
0-1	14(73.6)	5(26.4)	19(18.2)
1-2	9(45)	11(55)	20(19.2)
2-3	13(68.4)	6(31.5)	19(18.2)
3-4	11(42.3)	15(57.7)	26(25)
4-5	10(50)	10(50)	20(19.2)
Total	**57(54.8)**	**47(45.2)**	**104(100)**

The study population comprises 54.8% male and 46% female, there is no significant difference (p = 0.3276) in male female distribution when we consider study population in total (Table 2). Of these in infancy there is male predominance , 14 out of 19 were male constituting 73.6% of the total population in infancy.

Out of 104 children, 19 (18.2%) were less than 1 year of age ; 20(19.2%) belonged to the age group 1 to 2 years ;19 (18.2 %) to the age group 2 to 3 years ; 26 (25 %) to the age group 3 to 4 years ; 20 (19.2 %) children to the age group 4 to 5 years.

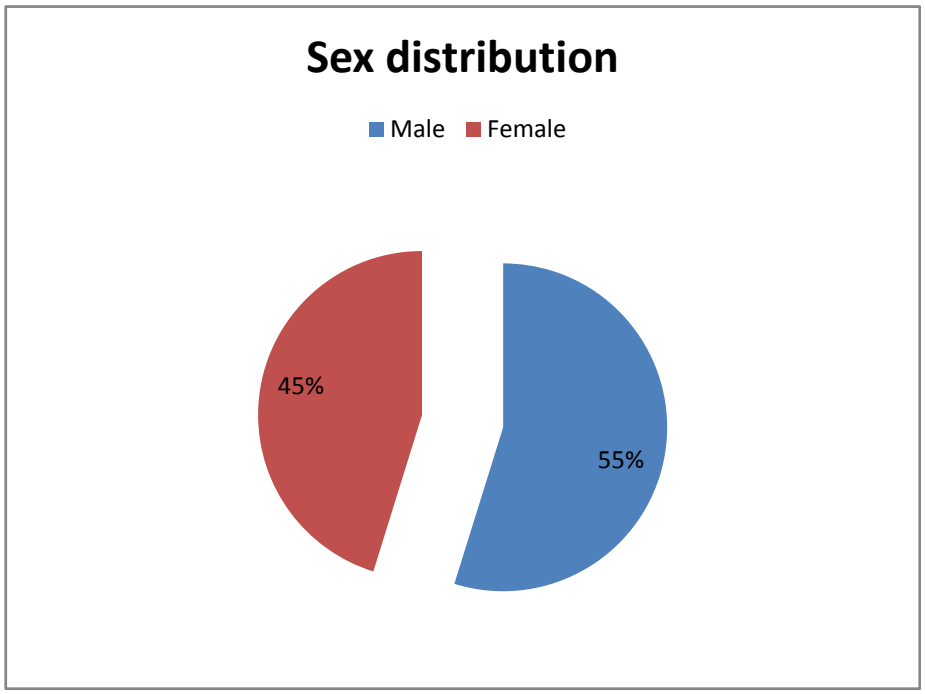

Fig 3 Sex distribution in recurrent wheezers less than 5 years

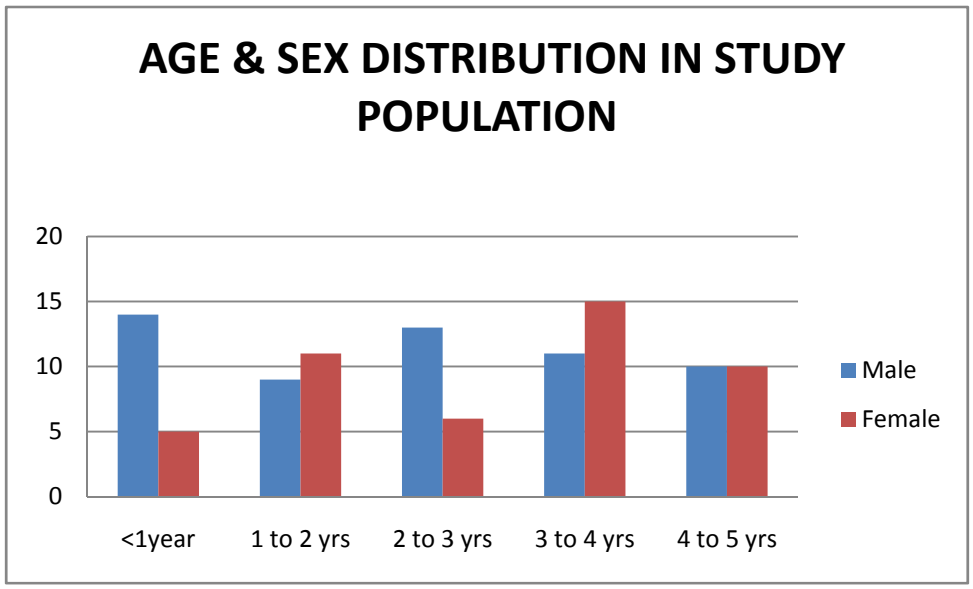

Fig 4 Age and sex distribution in children with recurrent wheeze

Table 3 Age of onset of symptoms in the study population

Age of onset	0 to 1 year n = 19 n(%)	1 to 2 years n = 20 n(%)	2 to 3 years n = 19 n(%)	3 to 4 years n=26 n(%)	4 to 5 years n = 20 n(%)	Total n =104
Since birth	5(26.4)	0	0	0	0	5(4.8)
<1 year	14(73.6)	10(50)	9(47.3)	7(26.9)	1(5)	41(39.4)
>1 year	0	10(50)	10(52.6)	19(73.1)	19(95)	58(55.7)

In the study population ,5(4.8%) had symptoms since birth, 41 (39.4 %) had onset of symptoms less than 1 year of age and 58(55.7 %) had symptoms onset after 1 year of age (Table 3).

Table 4 Clinical features among children with recurrent wheeze

Clinical features	0 to 1 year n =19 n(%)	1 to 2 years n = 20 n(%)	2 to 3 years n =19 n(%)	3 to 4 years n = 26 n(%)	4 to 5 years n = 20 n(%)	Total n = 104 n(%)
Cough	18(94.7)	18(90)	19(100)	26(100)	17(85)	98(94.2)
Fever	9(47.3)	10(50)	12(63.2)	7(26.92)	2(10)	36(34.6)
Noisy breathing	12(63.1)	5(25)	0	4(15.3)	1(5)	22(21.1)
Snoring	5(26.4)	2(10)	1(5.2)	1(3.8)	1(5)	10(9.6)
Triggers	0	5(25)	9(47.3)	15(57.6)	15(75)	44(42.3)
Viral induced	10(52.6)	10(50)	12(63.2)	7 (26.9)	2(10)	37(35.57)

In addition to wheeze and breathlessness , 98(94.2%) presented with cough, 36 (34.6%) had associated fever, 22(21.1%) had noisy breathing, 10(9.6%) had snoring, particularly in infants 12(63.1 %) had noisy breathing and 5(26.4 %) had snoring.44(42.3%) had triggers in the form of exposure to cold, consumption of ice cream, chocolate, etc.37(35.57%) of the children wheeze during viral illness (Table 4).

Table 5 Personal and family history of atopy in the study population

ATOPY	0 to 1 year n= 19 n(%)	1 to 2 years n= 20 n(%)	2 to 3 years n=19 n(%)	3 to 4 years n= 26 n(%)	4 to 5 years n= 20 n(%)	Total n=104 n(%)
Eczema	1(5.2)	2(10)	2(10.4)	5(19.2)	1(5)	11(10.57)
Rhinitis	1(5.2)	3(15)	2(10.4)	6(23)	4(20)	16(15.38)
Family H/o Atopy	3(15.7)	7(35)	6(31.5)	12(46.1)	10(50)	38(36.53)

Table 5 shows 11(10.57%) of the study population had eczema, 16(15.38%) had rhinitis,38 (36.53%) had family history of atopy.

Table 6 Response to short acting beta analogue among children with recurrent wheeze

Response to SABA	0 to 1 year n= 19 n(%)	1 to 2 years n=20 n(%)	2 to 3 years n=19 n(%)	3 to 4 years n=26 n(%)	4 to 5 years n=20 n(%)	Total n=104 n(%)
Good	4(21)	17(85)	17(89.47)	26(100)	20(100)	84(80.77)
Partial	5(26.4)	2(10)	0	0	0	7(6.7)
Poor	10(52.6)	1(5)	2(13.3)	0	0	13(12.5)

84(80.77%) children with recurrent wheeze had good response to short acting beta analogue, whereas among infants only 4(21%) had good response to SABA ,15(79 %) had either partial or poor response to SABA(Table 6)

Table 7 Causes of recurrent wheeze and phenotypes of asthma in children below 5 years

Age	Episodic wheeze	Multitrigger Wheeze	Asthma	Airway anomaly	Retained foreign body	GERD	Others
0 to 1 year	4*	0	0	14	0	0	1
1 to 2 years	10	2	3	4	1	0	0
2 to 3 years	7	7	2	2	1	0	0
3 to 4 years	6	12	5	2	0	1	0
4 to 5 years	2	15	3	0	0	0	0
Total	29(27.88)	36(34.6)	13(12.5)	22(21.15)	2(1.9)	1(0.9)	1(0.9)

* 1 case had associated laryngomalacia.

36(34.6%) were multitrigger wheezers,29(27.88%) were episodic wheezers, 22(21.15%) airway anomaly, 13(12.5%) asthma, 1.9% retained foreign body , 0.9% GERD. Airway anomaly predominates in infancy(15) (Table 7)

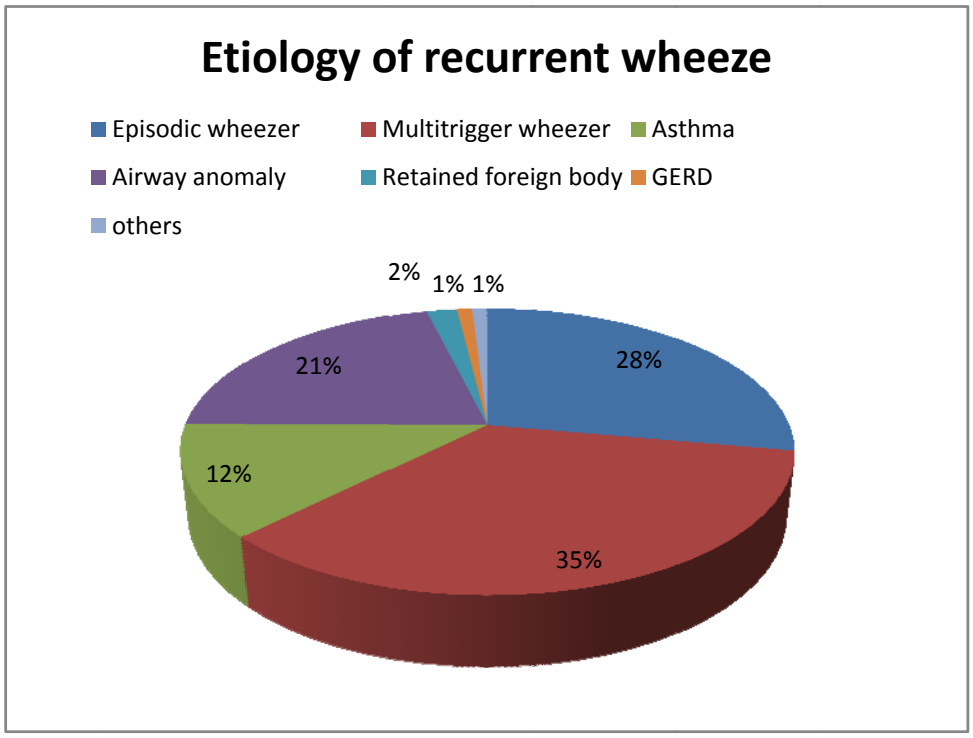

Fig 5 Etiology of recurrent wheeze in the study population

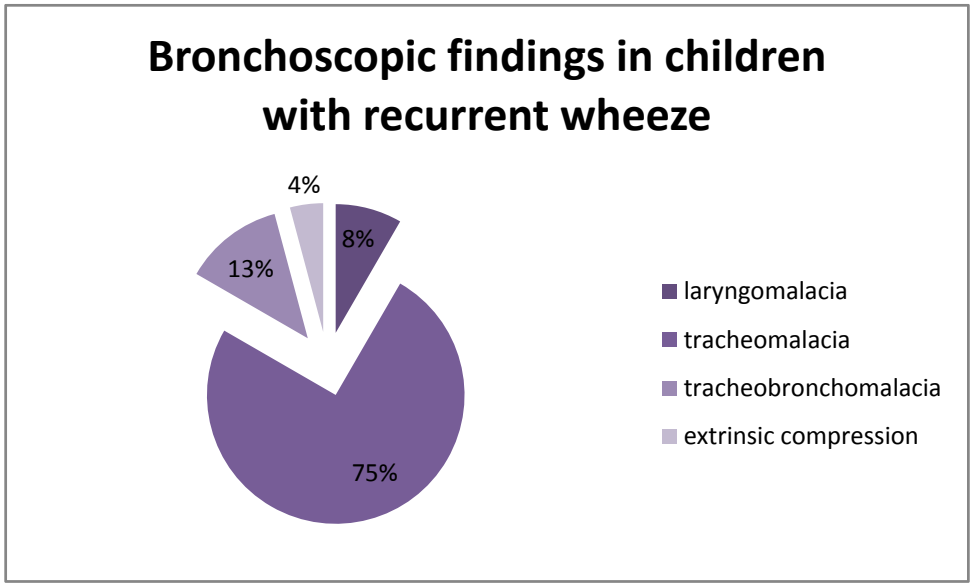

Fig 6 Bronchoscopic findings in children with recurrent wheeze

Out of 23 abnormal bronchoscopy findings 2(8%) had laryngomalacia of which 1 patient had associated tracheal stenosis, 18(75%) had tracheomalacia, 3(13%) had tracheobroncho- malacia, 1(4%) had extrinsic compression (Fig 6 , 8)

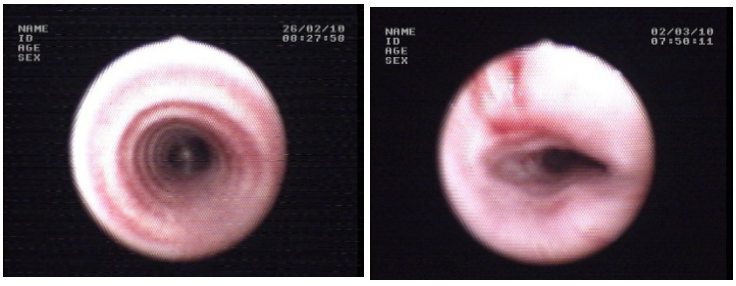

Fig 7 Bronchoscopic picture showing normal trachea and tracheomalacia .

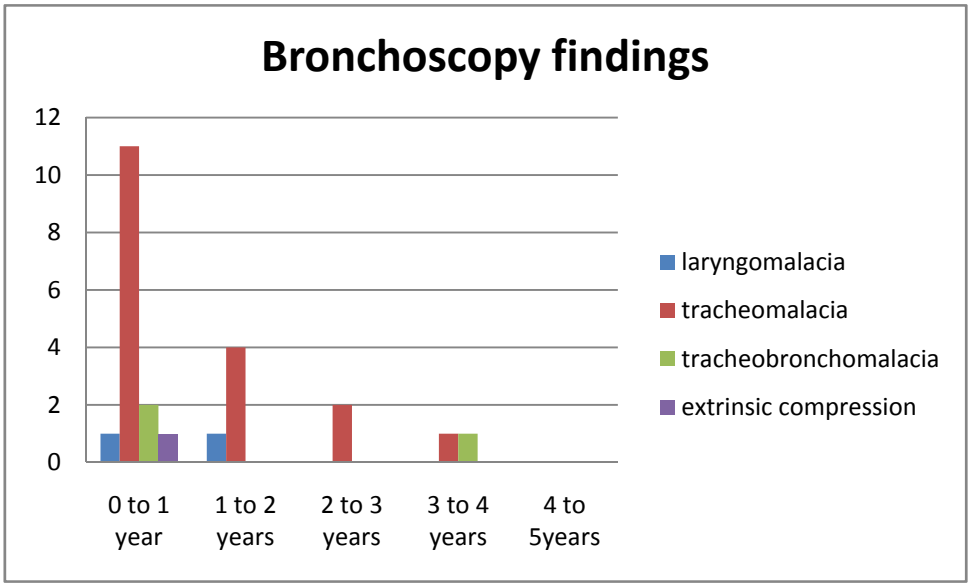

Fig 8 Age wise distribution of bronhoscopic abnormalities in children with recurrent wheeze

Table 8 Environmental factors associated with recurrent wheeze

Exposure	Episodic wheezer	Multitrigger wheezer	Asthma	Airway anomaly	Total 104
Passive smoking	6	7	2	7	22(21.1)
Exposure to pollen	0	2	1	0	3(2.8)
Exposure to industry	0	1	1	0	2(1.9)
Viral associated	29	4	0	7	40(38.4)

22(21.1%) of recurrent wheezers had exposure to passive smoking, 3(2.8 %) had exposure to pollen , 2(1.9%) had industrial exposure,

40(38.4 %) had wheeze associated with viral infection of which most of them belong to episodic wheezer (Table 8).

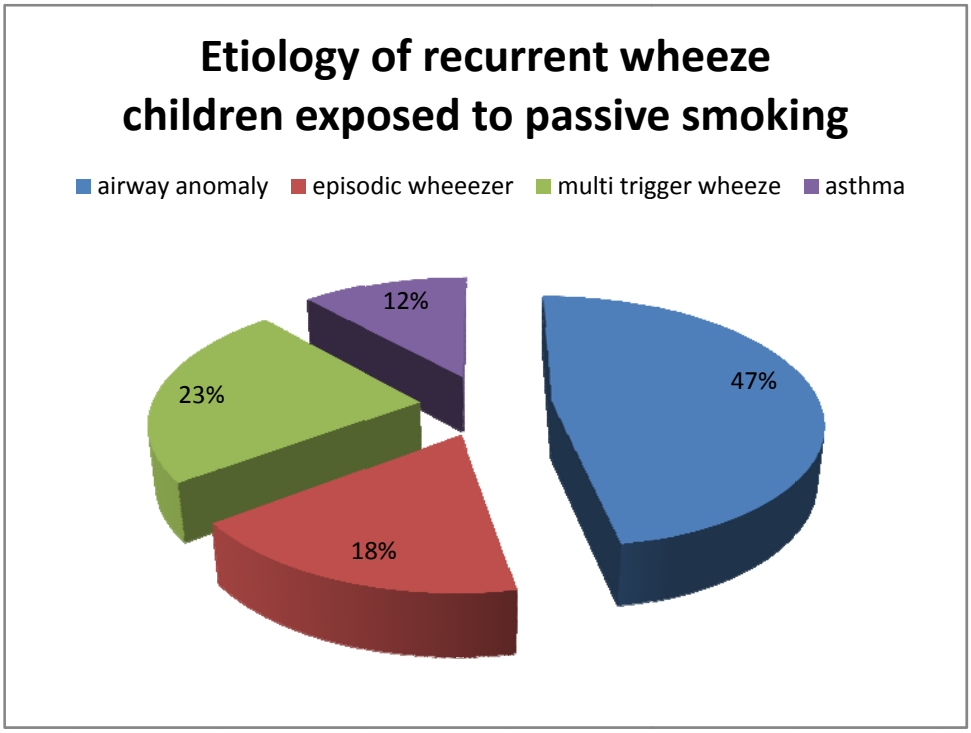

Fig 9 Etiology of recurrent wheeze in children exposed to passive smoking

Table 9 Recurrent wheeze and associated neonatal history

Neonatal history	Airway anomaly n(%)	Episodic wheezer n(%)	Multi trigger wheezer n(%)	Asthma n(%)	Total n(%)
Preterm	1(25)	2(50)	0	1(25)	4(3.8)
LBW	6(37.5)	4(25)	4(25)	2(12.5)	16(15.3)
HIE	1(50)	1(50)	0	0	2(1.9)
Respiratory distress	2(100)	0	0	0	2(1.9)
Other causes of hospitalisation	5(50)	3(30)	0	2(20)	10(9.6)

4(3.8%) of the study population were preterm, 16(15.3 %) low birth weight , 2(1.9 %) had birth asphyxia , 2(1.9 %) had respiratory distress in the new born period , 10(9.6%) were hospitalised in the neonatal period(Table 9)

Table 10 Clinical profile in various etiology

Clinical features	Episodic wheezer n=29 n(%)	Multitrigger wheezer n=36 n(%)	Asthma n=13 n(%)	Airway anomaly n=22 n(%)
Sex				
Male	14(48.2)	17(47.2)	7(53.8)	17(77.2)
Female	15(51.8)	19(52.78)	6(46.2)	5(21.7)
Age of onset				
Since birth	0	0	0	5(21.7)
<1 year	11(37.9)	10(27.78)	6(46.2)	14(60.8)
>1 year	18(62)	26(72.2)	7(53.8)	4(28.5)
Cough	29(100)	33(91.6)	13(100)	20(86.9)
Fever	29(100)	4 (11.11)	0	7(30.4)
Noisy breathing	5(17.2)	3(8.3)	0	14(60.8)
Snoring	1(3.4)	2(5.5)	0	7(30.4)
Eczema	0	2(5.5)	8(61.5)	1(4.3)
Rhinitis	0	3(8.3)	11(84.6)	2(8.6)
Family H/o Atopy	5(17.2)	17(47.2)	13(100)	3(13.04)
Triggers	0	36(100)	13(100)	0
Response to SABA				
Good	29(100)	36(100)	13(100)	4(17.3)
Partial	0	0	0	7(30.4)
Poor	0	0	0	11(50)

Episodic wheezers had cent percent association with viral induced wheeze and fever, multitrigger wheezers have 100 % association with other triggers like exposure to cold, sweet, etc, asthma group has in addition to triggers personal atopy in the form of eczema 8(61.5%) , rhinitis 11(84.6 %), family history of atopy

100 %. Airway anomaly group is associated with early onset < 1 year (19) 82.5 % noisy breathing 14(60.8 %), snoring 7(30.4%) , poor or partial response to SABA (18)72.57 %.

Clinical features in various etiology of recurrent wheeze

Out of the 29 children with episodic wheeze, 14(48.2%) were male and 25 (51.8%) showing no sex predilication. 11(37.9 %) had onset before 1year and 18 (62%) had onset after 1 year . None had symptoms since birth. All 19 children had fever , cough , 5 (17.2 %) had noisy breathing , 1(3.4%) had snoring , none had personal atopy, 5 (17.2 %) had family H/O atopy. All of them had wheeze in response to viral infection and all of them responded well to SABA.

Out of 36 children with multitrigger wheeze 17 (47.2 %) were males, 19(52.78%) were females showing no sex difference. 10 (27.78%) had onset of symptoms before 1 year of age and 26 (72.2 %) had onset of symptoms after 1 year of age.33(91.6%) had cough , 4(11.11%) had fever ,3(8.3%) had noisy breathing , 2 (5.5%) had snoring , 2(5.5%) had eczema , 3 (8.3 %) had rhinitis , 17 (47.2 %) had family H/O atopy , 4(11.11%) wheeze associated with viral

infection , all of them had triggers other than viral infection and all of them responded well to SABA.

Out of 22 children with asthma 7(53.8%) were males, 6(46.2 %) were females showing no sex difference.6(46.2%) had onset of symptoms before 1 year of age and 7 (53.8 %) had onset of symptoms after 1 year of age.All of them had cough , none had fever noisy breathing , snoring , 8(61.5%) had eczema , 11 (84.6 %) had rhinitis , all had family H/O atopy , all of them had triggers other than viral infection and all of them responded well to SABA.

Out of 13 children with airway anomaly 18(78.2 %) were male, 5 (21.7 %) were female showing a male predisposition. 5(21.7%) had onset since birth, 14 (60.8 %) had onset of symptoms before 1 year of age, 4 (28.5%) had onset of symptoms after 1 year of age, 20 (86.9 %) had cough, 7 (30.4 %) had fever, 14 (60.8 %) had noisy breathing, 7(30.4 %) had snoring, 19 (82.5%) had either poor or partial response to SABA.

Table 11 Comparision between airway anomaly and recurrent wheezers with no airway anomaly (episodic wheezer, multitrigger wheezer, asthma)

Clinical features	Airway anomaly n=23 n(%)	No airway anomaly n=77 n(%)	P value
Sex			
Male	18(78.2)	38(49.4)	0.0164
Female	5(21.7)	40(50.6)	0.0160
Age of onset			
<1 year	19(82.5)	27(35.06)	0.001
>1 year	4(28.5)	51(66.3)	0.017

Airway anomaly which contributed to 22.11% of recurrent wheezers differ in sex distribution with significant male preponderance (p = 0.0164) and significant proportion with onset < 1 year among wheezers with airway anomaly (p = 0.001) (Table 11)

Table 12 Comparison of clinical features in children with airway anomaly and no airway anomaly

Clinical features	Airway anomaly n=23 n(%)	No airway anomaly n=77 n(%)	P value
Cough	20(86.9)	75(97.4)	0.04
Fever	7(30.4)	29(37.6)	0.5086
Noisy breathing	14(60.8)	8(10.3)	0.0001
Snoring	7(30.4)	3(3.8)	0.0003
Eczema	1(4.3)	10(12.9)	0.2487
Rhinitis	2(8.6)	14(18.2)	0.2731
Family H/o Atopy	3(13.04)	35(45.45)	0.0060
Response to SABA			
Good	4(17.3)	78(100)	0.0001
Partial/poor	19(82.57)	0	0.0001

In children with airway anomaly the predominant symptoms were noisy breathing and snoring and they are statistically significant.Children with other wheezing phenotpes have triggers and family H/O atopy and the association is statistically significant.

Children having airway anomaly respond to SABA either partially or poorly in comparison with other wheezing phenotypes and the difference is statistically significant (Table 12).

DISCUSSION

A descriptive study was conducted at Institute of Child Health to find out the demographic characterstics , Clinical profile and etiology of recurrent eheeze in children less than 5 years of age. 104 children less than 5 years of age getting admitted at Institute of child health who met the inclusion and exclusion criteria were recruited. We had 29 (27.88%) episodic wheezers, 36 (34.6 %) multitrigger wheezers, 13(12.5 %) asthma, 23(22.11%) airway anomaly, 2 (1.9%) retained foreign body, 1(0.9 %) GERD.

In our study 57 were males and 47 were females showing no difference sex wise but in age less than 1 year there was male preponderance. Patra S , et al report in children less than 2 years there was male predominance among wheezers 9:2 which is consistent with our study (17). . LY et al found no significant difference in gender in early onset wheeze (< 3 years) (22).

Mathieu F *et al* found a high prevalence of atopy in children with recurrent wheeze who are at risk of developing asthma (16). Our study also shows a high association between atopy and wheeze ,

17.2 % of episodic wheezers had family history of atopy,47.2 % of multitrigger wheezers had family H/O atopy , 100% of asthmatics had family H/O atopy , 61.5 % had personal H/O eczema and 84.6 % had H/O allergic rhinitis.

Litonjua *et al* showed that odds of having a child with asthma is high with parental history of asthma (23).This is consistent with our study which shows 100 % association of family H/O atopy in asthmatics.

Cough, which is barking or brassy,and expiratory stridor are the most common symptoms (24). In case of extrathoracic tracheomalacia of the, there can be inspiratory stridor. The cough is in tracheomalacia is due to juxtaposition of the anterior and posterior walls of the trachea, which causes irritation and recurrent vibrations of the airway. Affected children may have noisy breathing which can either high pitched or low pitched. Our study also shows that noisy breathing (60.8 %) is the predominant symptom in airway anomaly.

Dirk E Boc. *et al* emphasizes the need to reconsider the diagnosis in children with features suggestive of airway obstruction

who do not or partially respond to bronchodilators (25).This is rightly pointed by our study which also states that82.6% of children with airway anomaly respond either poorly or partially to bronchodilators.

RubenB, *et al* (10) reported primary airway malacia in 136 children (80 male) with a median (range) age of 4.3 (0 to 17) years (male/female ratio, 1.4:1) (10). This is consistent with our study in which there is male predominance in children with airway anomaly.

Table 13 Comparison of airway anomalies with previous study

	Ruben B *et al*	Present study(airway anomaly group)
Sample size	136	23
Study population	0 to 17 years	0 to 5 years
Male/female ratio	1.4:1	3.6:1
Larymgomalacia	0	2(8.6)
Tracheomalacia	63(46)	18(78.2)
Tracheobronchomalacia	49(36)	2(13.04)
Bronchomalacia	24(18)	0
External compression	0	1(4.3)

Our study shows a predominance of tracheomalacia comparing to the study by Ruben B *et al* which could be due to the difference in sample size and the age group which is different in our study.

S. Saglani, *et al* (12) in his study on recurrent wheeze in children between 3 months and 5 years, the comparison shown in Table 14.

Table 14 Comparison of etiology of recurrent wheeze with previous study

	Saglani S *et al*	Present study
Sample size	47	104
Study population	3months to 5 years	0 to 5 years
Airway anomaly	13(27.6)	23(22.11)
Asthma	19(40.4)	13(12.5)
Viral associated wheeze / episodic wheezer	6(12.7)	29(27.88)
Multitrigger wheezer		36(34.6)
GERD	11(23.4)	1(0.9)
Others	11(23.4)	2(1.9)

The previous study is based on investigations which may not be possible in a resource poor setting like ours whereas our study is mainly based on clinical features. Incidence of airway anomaly is consistent with the previous study. Viral associated wheeze is less than in our study. This could be explained by the fact that the previous study was conducted at London where infection rate is less than our population.Incidence of asthma is very high in the previous study but they have not attempted to separate multitrigger wheezers.

In our study both asthma and multitrigger wheezer put together constitutes 47 % which is consistent with the previous study. GERD is very high in their study compared to our study, which could be due to the associated airway anomaly.

LIMITATIONS

- The sample size is small.
- The study was done at a tertiary care centre , so the study population does not reflect the general population.

CONCLUSION

1. In children less than 5 years asthma is not the only cause of recurrent wheeze.

   The various etiologies are as follows:

   Episodic wheeze 27.88 % ,Multitrigger wheeze 34.6%, Asthma 12.5 % , Airway anomaly 21.11 %, Retained Foreign body 1.9 % GERD 0.9%, Others(0.9%)

2. Episodic wheezers were usually associated with wheeze during viral illness and they were asymptomatic in between.

3. Multitrigger wheezers have wheeze due to various other triggers and some of them had family history of atopy.

4. Of the multitrigger wheezers who had personal atopy wre classified as asthma.Asthma can be diagnosed clinically only based on history in children less than 5 years.

5. Wheeze which is due to airway anomaly differ not only in their clinical presentation but also in response to treatment, hence wheeze which is difficult to control warrants further evaluation.

RECOMMENDATIONS

- In case of wheeze which is difficult to treat it is recommended to take a detailed history which clinches the diagnosis in many cases.
- In case of infants bronchoscopy may be recommended.

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DATA COLLECTION FORM

A. Patient details:

- Name
- Age
- Sex
- Ward / IP No:
- Address

- Socioeconomic status

B. History

- Onset
- Cough
- Fever
- Breathlessness
- Wheeze

- Noisy breathing snoring
- Snoring
- Recurrent aspiration
- Foreign body aspiration
- Contact
- Similar episodes in past
- Hospitalisation
- H/O nebulization
- Response to bronchodilator
- H/O eczema
- H/O rhinitis

C. Perinatal History:

- Term or preterm
- Birth weight
- Birth asphyxia
- Respiratory distress
- Hospitalisation (if yes what intervention

D. Feeding History

- Breastfeeding initiated ?
- Exclusive breast feeding ?
- How long Breastfed ?

E. Developmental History

F. Environmental history

- Passive smoking
- Exposure to allergens or pollens
- Any industry nearby

G. Family history

- Eczema
- Rhinitis
- Asthma

H. Nutrirtional status:

- Height or length
- Weight
- BMI

I. Investigations:

- Blood count
- Chest X ray
- X ray paranasal sinus
- Barium swallow
- Bronchoscopy

ABBREVIATIONS

RSV	–	Respiratory Syncitial Virus
GER	–	Gastro Esophageal Reflux Disease
BAL	–	Broncho Alveolar Lavage
ICH & HC	–	Institute ofChild Health and Hospital for Children
WALRI	–	Wheeze Associated Lower Respiratory Tract Infection
TEF	–	Tracheo Esophageal Fistula
SABA	–	Short Acting Beta Analogue

INFORMED CONSENT FORM

I agree to participate in the study titled epidemiology, clinical profile and etiology of recurrent wheeze in children below 5years

I confirm that I have been told about this study in my mother tongue (Tamil) and I had the opportunity to ask question. I confirm that I have been told about the risk and potential benefits of my child's participation.

I understand that my child participation is voluntary and I may refuse to continue at any time without giving any reason if i think my child's benefit is being affected.

I agree not to restrict the use of any data or results that arise from this study.

1. Name of the child :
2. Name of guardian/care giver :
   Signature :
   Date :
3. Name of the witness :
   Signature :
   Date :
4. Name of investigator :
   Signature :
   Date :

தகவல் தாள்

ஆய்வின் நோக்கம்

ஐந்து வயதிற்கு உட்பட்ட குழந்தைகளில் மீண்டும் மீண்டும் இளைப்பு வருவதற்கான காரணம் மற்றும் இக்குழந்தைகளின் நோயின் தன்மைகளையும் அறிவதே இந்த ஆய்வின் நோக்கம்.

சட்டத்தினால் வழங்கப்பட்ட விவரம் இரகசியமாக பாதுகாக்கப்படும். இந்த ஆய்வில் தங்கள் குழந்தை பங்கேற்பது உங்களது விருப்பத்தைப் பொறுத்தது. இந்த ஆய்வில் இருந்து விலகுவதால் மருத்துவ சிகிச்சை அளிப்பதில் எந்தவித இடையூறும் நேராது. ஆய்வில் பங்கேற்கும் போது இடையில் விலகவோ, கேள்விகளுக்கு விடையளிக்காமல் இருக்கவோ தங்களுக்கு உரிமை உள்ளது.

ஆய்வு குறித்து தங்களுக்கு ஏதேனும் சந்தேகம் நேரிடின் ஆய்வாளரை நேரில் சந்திக்கவோ, தொலைபேசியில் தொடர்பு கொள்ளவோ வரவேற்கப்படுகிறீர்கள்.

அபாயங்கள் மற்றும் நன்மைகள்

இந்த ஆய்வில் பங்கேற்பதால் எந்தவித தீங்கும் ஏற்பட வாய்ப்பில்லை. இதில் பங்கேற்கும்போது செய்யப்படும் மருத்துவ பரிசோதனைகள் மற்றும் சிகிச்சை முற்றிலும் இலவசமானது.

ஒப்புதல் படிவம்

இந்த ஆய்வில் செய்யப்படுகின்ற செய்முறைகளினால் ஏற்படும் பக்க விளைவுகளுக்கு மருத்துவ உதவி செய்யப்படும். எந்தவித நஷ்ட ஈடும் தரப்படாமாட்டாது என்பதையும் அறிந்து கொண்டேன்.

1. நான் இந்த ---------- தேதியிட்ட தகவல் படிவத்தை நன்றாக படித்து. படித்துக் காட்டி எடுத்துரைத்ததை புரிந்து கொண்டேன். எனக்கு கேள்வி கேட்கும் வாய்ப்பும் கிடைத்தது.
2. இந்த ஆய்வில் நான் என்னுடைய சுய அறிவோடு பங்கு கொள்கிறேன். மேலும் இந்த ஆய்விலிருந்து எந்த வித காரணமும் தராமல் மருத்துவப் பரிசோதனையிலிருந்து நான் விலகிக் கொள்ளலாம். இதனால் சட்ட ரீதியான எந்த செயலும் உட்படுத்தாது.
3. Ethics குழுவின் அங்கத்தினர்களோ. இந்த ஆய்வை நடத்துபவர்களோ என்னுடைய மருத்துவ ஆய்வின் அனைத்து விவரங்களையும் என்னுடைய அனுமதியின்றி பார்க்கவோ. படிக்கவோ உரிமையுள்ளவர்களாவர். நான் இந்த ஆய்விலிருந்து விலகிக் கொண்டாலும் கூட என்னுடைய விவரங்களை அவர்கள் அறிந்து கொள்ள ஒத்துக் கொள்கிறேன். என்னுடைய விவரங்கள் அனைத்தும் 3வது நபருக்கோ அல்லது பத்திரிக்கையில் வெளியிடுவதற்கோ முயலமாட்டார்கள் என நம்புகிறேன்.
4. இந்த ஆய்விலிருந்து பெறப்பட்ட புள்ளி விவரங்களையோ அல்லது முடிவுகளையோ பயன்படுத்தக் கூடாது என்று கட்டுப்படுத்த மாட்டேன்.
5. என் குழந்தையை இந்த மருத்துவ ஆய்விற்கு பங்கு கொள்ள பரிபூரணமாக சம்மதிக்கிறேன்.

கையொப்பம்.....தேதி.....

பெயர்.....

குழந்தையின் பெயர்.....

ஆய்வாளர் கையொப்பம் தேதி :

சாட்சிகள் கையொப்பம் தேதி :